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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/926,576	09/09/97	HAENSLER J	0725.0100000

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EXAMINER	
BRUMBACK, B	
ART UNIT	**PAPER NUMBER**
1642	21

DATE MAILED: 03/07/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/836,576	Applicant(s) Haensler et al.
	Examiner Brenda Brumback	Group Art Unit 1642

☒ Responsive to communication(s) filed on *Jan 6, 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *25-86* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *25-86* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The request filed on 01/06/2000 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/836,576 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 25-88 are pending.

Specification

3. The disclosure is objected to because of the following informalities

A title for the description of the drawings is required. It is suggested that the title "Brief Description of the Drawings" be inserted at page 6, between lines 20 and 21.

It is suggested that tables 1 and 2, which appear on page 12 of the disclosure, be removed from the main body of the disclosure and submitted as figures.

Claim Rejections - 35 USC § 112

4. Claims 47 and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claims recite a proportion of lipid to adjuvant of 20%. Since a

proportion is normally written as a ratio instead of a percentage, either the term "proportion" should be amended to "concentration" or "20%" should be amended to a ratio.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

a. Claims 25-64, 66-78, and 80-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bolcsak et al. (U.S. Patent 5,100,662; of record as AC1 in Paper # 7) in view of Gao et al. (Biochem. Biophys. Res. Comm. 179:280-285, 1991; of record as AS1 in Paper #7).

The claimed invention is drawn to a vaccine composition comprising at least one antigen and at least one amphipathic adjuvant possessing a lipophilic group derived from a sterol, or specifically from cholesterol, linked to a cationic group via a carbamoyl group, for administration simultaneously, separately, or staggered over time. Dependent claims either recite the lipophilic group of the adjuvant as a cholesterol derivative, the cationic group as a quaternary ammonium or amine which can be protonated, and separation of the lipophilic and cationic groups by a branched or unbranched alkyl chain comprising 1-20 carbon atoms; or they specifically recite the adjuvant as selected from cholesteryl-3β-carboxamidoethylenetrimethylammonium iodide, cholesteryl-3β-

carboxamidoethyleneamine, cholesteryl-3β-oxysuccinamidoethylene-trimethylammonium iodide, 3β-(N-(N'-dimethylaminoethane)carbamoyl)cholesterol, and 3β-(N-(polyethylenamine)carbamoyl)cholesterol. Dependent claims also recite that the antigen is an influenza virus hemagglutinin antigen; that the composition further comprises a neutral lipid in a proportion greater than 20%, that the neutral lipid is dioleoylphosphatidylethanolamine or dioleoylphosphatidylcholine; and recite that the adjuvant is dispersed in an aqueous environment in the form of liposomes which include the antigen. Dependent claims are also drawn to a method of making the composition comprising combining the antigen and the adjuvant and to methods of inducing an immune response (cytotoxic T cell or humoral) in a mammal by administering the vaccine composition by the subcutaneous, mucosal, or intranasal route.

Bolcsak et al. teach vaccine compositions comprising an antigen entrapped within a liposome which comprises a derivatized sterol, and specifically derivatized cholesterol, linked to a charged group as an adjuvant (see column 5, lines 5-41; column 6, lines 51-54; and column 11, lines 37-38). Bolcsak et al. teach a preferred embodiment of the immunizing antigen as influenza virus hemagglutinin (column 6, lines 26-38). Bolcsak et al. also teach an embodiment comprising the derivatized sterol in combination with a second lipid (DMPC; see column 6, lines 45-65) in a molar ratio of 80:20 to 20:80. Bolcsak et al. teach administration of the liposomes and antigen either simultaneously or separately over time (column 8, lines 3-19) by any suitable route, including the mucosal, subcutaneous, and nasal routes (column 15, lines 24-31) in order to elicit both cytotoxic T-cell and humoral responses (see column 2, lines 24-46 and column 4, lines 22-

24). Bolcsak et al. teach that the core derivatized sterol or cholesterol molecule can be attached to the charged group via a number of different bridges, which include ester and alkyl bridges (methylene, ethylene, propylene, butylene, etc.), among others (see column 5, lines 22-26). Bolcsak et al. teach that the chemical linkage should be chosen to promote the stability of the liposomes during long periods of storage (see column 5, lines 42-47 and column 11, lines 56-64). The claimed invention differs from the composition disclosed by Bolcsak et al. in the recitation of the linkage or bridge as a carbamoyl group, in the recitation of dioleoylphosphatidyethanolamine or dioleoylphosphatidylcholine as the neutral lipid, and in the recitation of the derivatized cholesterol specifically as selected from cholesteryl-3β-carboxamidoethylenetrimethylammonium iodide, cholesteryl-3β-carboxamidoethyleneamine, cholesteryl-3β-oxysuccinamidoethylene-trimethylammonium iodide, 3β-(N-(N'-dimethylaminoethane)carbamoyl)cholesterol, and 3β-(N-(polyethylenamine)carbamoyl)cholesterol.

Gao et al. teach that liposomes prepared from the cationic derivative of cholesterol, 3β[N-(N', N'-dimethylaminoethane)-carbamoyl]cholesterol (DC-Chol) and dioleoylphosphatidylethanolamine (DOPE) at molar ratios of 4:6, 5:5, or 6:4 are less toxic than other liposomal preparations. Gao et al. also teach that synthesis of DC-Chol is a simple one-step procedure and that small liposomes of DC-Chol and DOPE are easily prepared (see pages 280-281, Abstract and first paragraph, and page 282, paragraph 1, under *Results and Discussion*). Finally, Gao et al. teach that DC-Chol, containing a carbamoyl bond, is much more stable than

similar amphiphiles with an ester bond (page 284, last 2 lines), while still being biodegradable once it is inside cells (page 285, lines 5-7).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted the liposome formulation taught by Gao et al. for the liposome formulations of Bolcsak et al., in order to prolong shelf-life and reduce toxicity of the liposomes in the vaccine composition.

b. Claims 25-64, 66-78, and 80-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Popescu et al. (EPA 0 356 339) in view of Epand et al. (U.S. Patent 5,283,185), both references of record as AL1 in Paper # 5 and in Paper # 6 respectively.

The claimed invention is as described *supra* in paragraph 5a.

Popescu et al. teach liposomal vaccine compositions comprising influenza virus hemagglutinin and adjuvants of dimyristolyphosphatidylcholine (DMPC)/derivatized sterol (cholesterol) at a ratio of 1:1 (see the abstract; page 2, first paragraph; and page 3, first paragraph). Popescu et al. teach producing an immune response by administering the vaccine composition by a suitable route, such as the subcutaneous or oral route, among others (page 9, last full paragraph). Popescu et al. teach the stimulated cells of the immune system as comprising T-lymphocytes, among others, and teach the immune response as humoral or cell-mediated (see page 2, lines 23-36). Popescu et al. teach administering the antigen and adjuvant either simultaneously or separately over time (page 4, line 62, through page 5, line 15). The claimed

invention differs from the composition disclosed by Popescu et al. in the recitation of a carbamoyl linkage between the derivatized sterol and lipid; in the recitation of dioleoylphosphatidyethanolamine or dioleoylphosphatidylcholine as the neutral lipid; and in the specific recitation of the derivatized cholesterol as cholesteryl-3β-carboxamidoethylenetrimethylammonium iodide, cholesteryl-3β-carboxamidoethyleneamine, cholesteryl-3β-oxysuccinamidoethylene-trimethylammonium iodide, 3β-(N-(N'-dimethylaminoethane)carbamoyl)cholesterol, or 3β-(N-(polyethylenamine)carbamoyl)cholesterol.

Epand et al. teach cationic amphiphiles comprising a lipophilic group derivatized from cholesterol, a linker bond of a carboxyamide or carbamoyl, a spacer arm of an alkyl chain, and a cationic amino group; and a co-lipid of phosphatidylcholine or phosphatidylethanolamine (see the abstract and column 14, lines 51-68). Epand et al. teach the cationic lipid as selected from the group consisting of cholesteryl-3β-carboxamidoethylenetrimethylammonium iodide, cholesteryl-3β-carboxamidoethyleneamine, cholesteryl-3β-oxysuccinamidoethylenetrimethylammonium iodide, 3β-{N-(N',N'-dimethylaminoethane)-carbamoyl]-cholesterol, and 3β-{N-(polyethyleneimine) carbamoyl]-cholesterol (column 3, lines 22-47; column 15, lines 16-27; and column 16, lines 1-26). Epand et al. teach that cationic amphiphiles with carbamoyl linker bond are much more stable in an aqueous solution than those with other types of bonds that have been used in the liposome art.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the mixed-lipid composition taught by Epand et al. in the

vaccine composition of Popescu et al. in order to obtain an improved adjuvant with greater stability in an aqueous vaccine composition.

c. Claims 65 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Bolcsak et al. in view of Gao et al., or Popescu et al. in view of Epand et al., as applied to claims 25-64, 66-78, and 80-86 above, and further in view of del Prete et al. (Trends in Microbiology 2(1):4-6, 01/1994; of record as AT2 in paper #17).

The claimed invention is drawn to a method for inducing an immune response in a mammal comprising administering at least one antigen and at least one amphipathic adjuvant compound comprising a lipophilic group derived from a sterol linked to a polar or cationic group via a carbamoyl group, wherein the immune response is a TH_1-type immune response.

As discussed *supra*, Bolcsak et al. and Popescu et al. teach inducing humoral and cellular immune responses, which include a cytotoxic T-cell response, in a mammal by administering an antigen and an adjuvant compound comprising a derivatized sterol linked to a charged group. Gao et al. and Epand et al. teach improved stability in aqueous solutions when the sterol is linked to the charged group via a carbamoyl linkage. Bolcsak et al. teach that antigens within charged liposomes are readily endocytosed (see column 6, lines 22-23). Popescu et al. teach that the derivatized sterol helps to potentiate the immune response to the antigen (see page 4, lines 50-52). Neither Bolcsak et al. in view of Gao et al., nor Popescu et al. in view of Epand et al., teach the immune response specifically as a TH_1-type immune response, as in the claimed invention.

Del Prete et al. teach that viral antigens activate cytotoxic T cells of the T_H1 type (see page 5, column 2, second full paragraph, and the paragraph bridging columns 2 and 3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the viral antigen described by del Prete in the stable liposomes taught by either Bolcsak et al. in view of Gao et al. or Popescu et al. in view of Epand et al. in order to formulate a vaccine composition which when administered would elicit an enhanced TH_1-type immune response to the viral antigen, through immunopotentiation and enhanced cellular uptake.

Conclusion

6. No claims are allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Paula Hutzell whose telephone number is (703) 308-4310. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1642 FAX telephone number is (703)-305-3014. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

BB
February 25, 2000

Brenda Brumback
Patent Examiner